REMARKS

Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, 114, 115, 117, and 119 are currently pending in this application. Claims 41, 57, and 119 have each been amended to recite that at least one of L_1 or L_2 is a polyethylene glycol having a molecular weight less than 2000 Daltons. Claims 116 and 118 have been withdrawn without prejudice. Applicants reserve the right to file one or more continuation, divisional or continuation-in-part applications to any withdrawn subject matter. No new matter has been added by the amendments.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 41, 44, 49-51, 54-57, 71, 115, and 117 are rejected on pages 4-5 of the Office Action under 35 U.S.C. § 102(b) as allegedly being anticipated by *Polymeric Materials Science and Engineering*, 1998, 79:471-472 to Belcheva *et al.* ("Belcheva") alone or as evidenced by U.S. Patent No. 4,640,835 to Shimizu *et al.* ("Shimizu") regarding the newly added limitation of polyethylene glycol having a molecular weight of less than about 2000 Daltons.

Claim 119 is rejected on pages 10-11 of the Office Action under 35 U.S.C. § 102(b) as allegedly being anticipated by Belcheva alone or as evidenced by Shimizu regarding the newly added limitation of polyethylene glycol having a molecular weight of less than about 2000 Daltons.

Applicants respectfully traverse each of these rejections for the reasons set forth herein.

As the Examiner is aware, to establish anticipation, a single prior art reference must disclose each and every limitation of a claim either expressly or inherently. *See Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998); *Standard Havens Prods., Inc. v. Gencor. Indus., Inc.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991); *Jamesbury Corp. v. Litton Indus., Inc.* 756 F.2d (Fed. Cir. 1985); *American Hospital Supply v. Travenol Labs.*, 745 F.2d 1 (Fed. Cir. 1984) (holding that prior art is anticipatory only if every element of the claimed invention is disclosed in a single item of prior art). There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991);

Carella v. Starlight Archery Co., 804 F.2d 135, 138 (Fed. Cir. 1986); *RCA Corp. v. Applied Digital Data Sys.*, 730 F.2d 1440, 1444 (Fed. Cir. 1984) (holding that anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference).

A. The Anticipation Rejection of Claims 41, 44, 49-51, 54-57, 71, 115, and 117 Should Be Withdrawn

According to the Office Action, Belcheva discloses water-soluble fluorescein polymer-peptide conjugates. The Office Action alleges that the peptide (Ps) is 5 amino acids in length; the polymer is polyethylene glycol (PEG) with a MW of either 2000 or 5000. The office action further alleges that the newly added limitation that the polymer of 'L_1' has 'the molecular weight of less than about 2000 Daltons' is interpreted to include the molecular weight of 2000 as supported by the limitation of claim 57. The Examiner further alleges that it is known in the art that polyethylene glycol (PEG) includes lower molecular weight, (*i.e.*, less than 2000), as evidence by Shimizu, which disclose that PEGs having the molecular weight that range from 200 to 20,000.

Applicants have amended claims 41 and 57 to recite that L_1 or L_2 is a polyethylene glycol having a molecular weight of less than 2000 Daltons. Thus, because Belcheva is directed to PEG having a molecular weight of 2000 or greater, for at least this reason, Belcheva fails to disclose each and every element of the claimed invention and therefore cannot anticipate the claims.

With regard to Shimizu, Applicants first point out that it is improper to combine references in a section 102 rejection. (*See, e.g., Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116 (Fed. Cir. 2002) holding "a single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art"). Applicants further note that Shimizu is directed to plasminogen activator derivatives comprising at least one polyalkylene glycol having a molecular weight of about 200-20,000. Shimizu says nothing about polyethylene glycol, much less the additional elements of the claims. Thus, Shimizu also fails to disclose each and every element of the claimed invention.

Therefore, the Applicants respectfully submit that the rejection of claims 41, 44, 49-51, 54-57, 71, 115, and 117 under 35 U.S.C. § 102(b) as allegedly being anticipated by Belcheva or Shimizu should be withdrawn.

B. The Anticipation Rejection of Claim 119 Should Be Withdrawn

According to the Office Action, Belcheva discloses water-soluble fluorescein polymer-peptide conjugates. The Office Action alleges that the peptide (Ps) is 5 amino acids in length; the polymer is polyethylene glycol (PEG) with a MW of either 2000 or 5000. The office action further alleges that the newly added limitation that the polymer of 'L_1' has 'the molecular weight of less than about 2000 Daltons' is interpreted to include the molecular weight of 2000 as supported by the limitation of claim 57. The Examiner further alleges that it is known in the art that polyethylene glycol (PEG) includes lower molecular weight, (*i.e.*, lest than 2000), as evidenced by Shimizu, which allegedly discloses PEGs having molecular weights that range from 200 to 20,000.

Applicants have amended claim 119 to recite that L_1 or L_2 is a polyethylene glycol having a molecular weight less than 2000 Daltons. Thus, because Belcheva is directed to PEG having a molecular weight of 2000 or greater, for at least this reason, Belcheva fails to disclose each and every element of the pending claims, and therefore cannot anticipate the claims.

As stated above, it is improper to combine Belcheva with Shimizu to contrive an anticipation rejection under 35 U.S.C. § 102(b). (*See, e.g., Verve, LLC*). Applicants again note that Shimizu is directed to plasminogen activator derivatives comprising at least one polyalkylene glycol having a molecular weight of about 200-20,000. Claim 119, as amended, recites a library consisting of a plurality of water-soluble peptidic substrates comprising, *inter alia*, polyethylene glycol less than 2000 Daltons. Thus, Shimizu fails to disclose each and every element of the claimed invention.

Therefore, the Applicants respectfully submit that the rejection of claim 119 under 35 U.S.C. § 102(b) as allegedly being anticipated by Belcheva alone or as evidenced by Shimizu should be withdrawn.

II. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, and 71 were rejected on pages 7-10 of the Office Action under 35 U.S.C. § 103(a) as allegedly obvious over Belcheva, Shimizu, and Pomroy *et al.*, *Biochemical and Biophysical Research Communications*, **1998**, 245(2), 618-621 ("Pomroy").

As the Examiner is aware, the Federal Circuit has set forth three basic criteria that must be met to establish a *prima facia* case of obviousness. First, there must have been at the time of the invention a motivation to combine or modify the teachings of the references cited. *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination); *see also In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art). Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka*, 490 F.2d 488 (CCPA 1974) (holding that to establish *prima facia* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure). Third, there must have been at the time of the invention a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-1208 (Fed. Cir. 1991), *cert. denied* 502 U.S. 856 (1991) (holding that obviousness requires references to show that there was, at the time of the invention, a reasonable expectation of success).

According to the Office Action, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to include in the water-soluble fluorescein polymer-peptide conjugates - a thioether linkage at the R_2 position and the "end" residues (*i.e.*, P_{Hc1} and P_{Hc2}) of the peptide having a different net charge as taught by Pomroy when used in the library of Belcheva. The Office Action further alleges that one of ordinary skill in the art would have been motivated to couple the peptide to the polyethylene glycol (PEG) by way of the cysteine. According to the Office Action, the "end" residues (*i.e.*, P_{Hc1} and P_{Hc2}) of the peptide have different net charges in the water-soluble fluorescein polymer-peptide conjugates of Belcheva for the advantage of providing a cleavable disulfide bond between the thiol-reactive PEG and the protein. The Office Action then alleges that one of ordinary skill in the art would have a reasonably expectation of success in the combination of Belcheva and Pomroy because Pomroy discloses the success of PEGylation of the peptide using PEG-a-Cys reagent. Applicants respectfully traverse this rejection.

Applicants have amended claim 41 and 119 to recite that L_1 and L_2 are each independently: a branched or unbranched, hydrophilic, water-soluble, uncharged PEG polymer and each of L_1 and L_2 are independently of molecular weight of less than 2000 Daltons. Applicants have amended claim 57 to recite that at least one of L_1 or L_2 is a polyethylene glycol having a molecular weight from about 230 to less than 2000 Daltons. None of the cited references, either alone or in combination, teaches or suggests each and every element of the claimed invention, wherein at least one of L_1 or L_2 is a polyethylene glycol having a molecular weight less than 2000 Daltons. Because Belcheva, Shimizu, and Pomroy do not disclose or suggest all of the elements of the pending claims, the claims cannot be obvious in view of these references.

As the Examiner is aware, "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *Carella v. Starlight Archery*, 804 F.2d 135 (Fed. Cir. 1986). Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine the teachings of Shimizu with either Belcheva or Pomroy to ascertain the claimed invention. Indeed, as the Examiner stated Belcheva discloses water-soluble fluorescein polymer-peptide conjugates, but is silent as to a polyethylene glycol having a

molecular weight less than 2000 Daltons. Moreover, the combination of Belcheva with Shimizu and/or Pomroy does teach or suggest the claimed invention. Pomroy discloses hydrophobic peptides wherein the peptide is coupled to the polyethylene glycol by way of a cysteine with a PEG-a-cys reagent. Pomroy also fails to disclose or suggest polyethylene glycol having a molecular weight less than 2000 Daltons. Thus, each of Belcheva and Pomroy are silent with regard to a polyethylene glycol having a molecular weight less than 2000 Daltons. Shimizu does not remedy the deficiencies of Belcheva or Pomroy. Shimizu is not even relevant to the Applicant's invention, thus one of ordinary skill in the art would clearly have no motivation to combine Shimizu with Belcheva and/or Pomroy.

It is well-established law that "[t]he combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a *prima facia* case of obviousness." *In re Oetiker*, 977 F.2d 1443, 24 USPQ 1443 (Fed. Cir. 1992). Shimizu is non-analogous art that cannot be used as a basis for rejecting the claims. Indeed, "[i]n order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker* at 1446. The claimed library recited in the instant application and the plasminogen activator derivatives disclosed in Shimizu are in completely different fields. The claimed library encompasses water-soluble peptidic substrates for use in enzymatic activity assays. The library is useful in protein kinase, phosphatase, and protease activity assays. In contrast, Shimizu discloses plasminogen activator derivatives for inhibiting the formation of thrombus. The derivative disclosed in Shimizu is a human-originated, non-immunogenic plasminogen activator, which is stable and exhibits prolonged fibrinolytic activity when administered to living bodies. Thus, Shimizu is clearly not within the field of applicant's endeavor. Furthermore, Shimizu is not reasonably pertinent to the particular problem with which applicant is concerned. Applicant is concerned with the problem of providing uniformly soluble and detectable peptide substrates, which can be used directly for screening with various enzymes. Thus, fully functional, detectable peptide substrates may be identified without the need for further modification for detection or use in drug development assays.

Meanwhile, Shimizu addresses the problem of identifying plasminogen activator derivatives, which are stable and retarded by inhibitors present in blood and hence achieve prolonged half-life in blood. It addresses the problem by developing derivatives of human-originated, non-immunogenic plasminogen activators, which overcome the above-noted drawbacks of the prior art techniques.

One of ordinary skill in the art would not look to plasminogen activator derivatives to solve problems overcome by the claimed library, which is useful in protein kinase, phosphatase, and protease activity assays.

Thus, Shimizu is nonanalogous art, and one of ordinary skill in the art would not look to Shimizu to combine its teachings with those of any other reference cited herein.

In view of the claim amendments and the failure of the references to teach or suggest each and every element of the claimed invention, Applicants respectfully submit that the legally required *prima facie* case of obviousness based on the disclosures of Belcheva, Shimizu and Pomroy is not present.

For at least the above reasons, Applicants respectfully request that the Examiner withdrawal the rejection of claims 41, 44, 49-52, 54-57, 59, 62, 64-66, and 71 under 35 U.S.C. § 103(a).

III. Conclusion

Respectfully, Applicants submit that the claims are now in condition for allowance, favorable consideration and a Notice of Allowance are earnestly solicited.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,
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